REMARKS

After the entry of this amendment, claims 1, 3, 5-15, 17-29, 76, and 123-125 are pending, of which claims 1, 3, 6, 8-15, 17-28, and 123-125 are under examination. Claims 5, 29, and 76 were withdrawn from examination as claiming non-elected subject matter of restriction requirement.

Specification

The Examiner objected to the specification alleging informalities of figure descriptions in the specification. Applicants respectfully submit that the specification adequately describes the figures. Figure 1 shows the results of the experiment described in Example 4 (indicated on page 46, line 10), Figure 2 shows the results of the experiment described in Example 3 (indicated on page 44, line 17), and Figure 3 shows the results of the experiment described in Example 7 (indicated on page 48, line 17). From the description of Examples 3, 4, and 7, and from the brief description of the figures at page 9, it is sufficiently clear that the all three experiments contrast implantation of collagen matrix in subcutaneous location and intramuscular location. As indicated at page 46, lines 19-21, intramuscular implantation was better than subcutaneous implantation; therefore, the filled bars represent the results from intramuscular implantation, and the open bars represent the results from subcutaneous implantation.

The axis of Figure 2 is time in days. This is consistent with the description of the figure on page 9, and with the fact that in Example 3, the specification points out that at times longer than 120 hours (i.e. 5 days) post-implantation, the OP-1 administration failed to induce bone.

The axis of Figure 3 is the age of the rats in months. This is indicated in the first paragraph of Example 7, where the adults are characterized as being 24 months old, and the juvenile rats are characterized as 1 month old.

For clarification, Applicants will submit corrected figures with additional legends based on the specification as formal drawings. No new matter is introduced by the correction, for all information can be found in the original specification as described above.

35 U.S.C. §112 second paragraph

The Examiner rejected claims 1, 3, 6, 8-15, 17-28, and 123-125 as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as their invention. With regard to what is accessible, claims 1, 3, and 125 were amended so that it is unambiguous that a local defect site is accessible to progenitor cells, not a mammal. With regard to the start point of 6 hours, Applicants respectfully point the Examiner's attention to the claim language, which recites "local defect site accessible to progenitor cells" and not "accessed by progenitor cells." A site accessible does not need to have been accessed. At page 11, line 15-19, the specification states that a "defect site" as contemplated herein can define any structural disruption in a tissue or organ requiring repair. Therefore, it is clear that 6 hours is measured from the time the defect site was created.

Given the definition above, claims 15 and 123 are dependent claims with a meaningful differentiation of the scope of the claims. As the Examiner points out, 6 hours after creation of a local defect, mesenchymal progenitor cells are generally available at the defect site; however, the cells may not be available after a certain amount of time. Indeed, the effectiveness of OP-1 to induce bone formation wanes beyond 3 days after creation of local defect site, as shown in Figures 2A-2C. It is also contemplated that once the wound has healed, the mesenchymal cells are not needed to the area of the wound, and would not be as available as before the wound has healed. Therefore, Applicants submit that this limitation is not redundant when read together with the limitation reciting 6 hours after creation of a local defect site.

The Examiner alleges the claims lack essential step of correlating the results of an assay with the determination. Without conceding the correctness of the Examiner's position, solely to advance prosecution of the application, Applicants have amended the claims in an effort to clarify them. Accordingly, Applicants believe the amended claims are definite, and respectfully request the rejection be withdrawn.

35 U.S.C. §112 first paragraph

The Examiner rejected claim 1, 3, 6, 8-15, 17-28, and 123-125 as allegedly failing to comply with enablement requirement. The Examiner alleges that no guidance is given as to

steps (a) creating a local defect site, and (b) administering a morphogen at least 6 hours after creating the local defect site. The Examiner further stated that the description at page 5, lines 18-21 implies progenitor cells are available to certain defect sites before 6 hours has passed since the creation of a local defect site.

Applicants respectfully traverse. The specification clearly describes what constitutes a local defect site and provides some examples, e.g.,at p. 5, lines 12 – 17; page 6, lines 1-6; page 9, line 27 – page 10, line 8. The term "defect" is defined in the specification as any structural disruption in a tissue or organ requiring repair (page 11, lines 15-16). As described in the specification, where protocols are not described in detail, these defect sites can be created using standard procedures for the organ or tissue of interest. (See, for example, Example 8, at page 48, line 29; Example 9, page 49, line 16; Example 10, page 50, line 21; Example 12, page 52, lines 4-5; Example 15, page 55, lines 12-13; Example 16, page 56, line 3.) As there are many standard method of creating specific wound known and accepted in the art, based on the disclosure of the specification, one skilled in the art can easily envision what constitutes a local defect site and how to create it.

With regard to the Examiner's observation that the definition of a permissive site contemplates accessibility of the site by progenitor cells, Applicants do not dispute that some progenitor cells may be found at the created defect site in less than 6 hours after the creation of the defect site. Applicants are claiming administration of a morphogen at least 6 hours after creating the local defect site. This condition of administration is supported by the specification at page 6, lines 8-9. The claims do not recite, and are not limited to administering morphogen "when progenitor cells are available." As disclosed in the specification, it is Applicants' observation that progenitor cells typically become available to a defect site at least by 6-24 hours post trauma. Therefore Applicants claim a likely time when progenitor cells are available to the defect site to administer a morphogen. While some examples describe administering morphogen even prior to creating a local defect site, this does not preclude Applicants selecting other disclosed matter as the subject matter of claims to be pursued.

Applicants would like to reiterate that the recitation of a "defect site accessible to progenitor cells" does not mean that the site is actually accessed by progenitor cells, or that 6

hours is required for the site to become accessible to progenitor cells. A permissive local defect site is inherently accessible to progenitor cells. Such a site will not be blocked off or dammed off, for example, by an intentionally placed barrier as a result of surgery or by scar tissue formation that will block progenitor cells from entering the defect site. Whether progenitor cells will access an accessible site depends on other physiological events such as secretion of chemokines and/or cytokines in sufficient concentration for progenitor cells to start mobilizing toward the defect site. The Examiner correctly states in the office action that the only way to interpret a negative result is by comparison to a positive control, which statement is true in many if not all screening or evaluation protocols. Applicants demonstrated that OP-1 is such positive control.

The Examiner alleges that the art does not recognize a uniform requirement of at least 6 hours for infiltration of significant numbers of progenitor cells into a site of damage. It is well settled that operability serves as a touchstone for enablement. It is respectfully submitted that the claim is in fact operable. Applicants have shown through various experiments that when a morphogen is administered systemically to a local defect site at time points beyond 6 hours, the effect of morphogen could be seen. As explained above, this provides for positive control, which test morphogen candidates can be compared with. Whether or not 6 hours is necessary or best relative to other time points, the invention can be practiced with useful results when a morphogen candidate is administered at least 6 hours after the creation of a local defect site. Accordingly, the claimed invention is fully enabled.

Applicants contend that these remarks obviate the above rejection and respectfully request that the Examiner reconsider and withdraw this ground of rejection.

In view of the above amendment and remarks, applicant believes the pending application is in condition for allowance.

Applicant believes no fee is due with this response. However, if a fee is due, please charge our Deposit Account No. 18-1945, under Order No. JJJ-P01-570 from which the undersigned is authorized to draw.

Dated: October 11, 2005

Respectfully submitted,

By _____

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